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## Genetically based reduced MAOA and COMT functioning is associated with the cortisol stress response

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These findings are consistent with earlier findings from the Walter *et al.*<sup>6</sup> imaging study in that the ZNF804A risk allele was in both studies associated (and in the same direction) with altered responsiveness in social cognition in healthy participants. The two studies also differed, however, in that we observed this association only for interpersonal attributional style but not for theory of mind. Specifically, the observed difference in personalising bias scores between risk allele carriers versus non-risk carriers suggests their increased tendency to attribute negative events to other people rather than to situational factors. Such differences in personalising bias—the tendency to blame others—have variously been associated with paranoid ideation, anger and learned helplessness.<sup>10</sup> However, observation of these differences in healthy participants but not in patients appears inconsistent with the hypothesis that illness risk is mediated via effects on social cognition. Support for that hypothesis would necessitate a similar effect in patients to that observed in healthy participants.

Following the argument that genetic effects are more penetrant—and hence more identifiable—in functional imaging studies than in behavioural studies, it is possible that ZNF804A's subtle effects on behavioural measures of social cognition in patients were missed, despite including twice as many patients as controls and six times as many participants overall as in Walter *et al.*<sup>6</sup> In particular, subtle effects on social cognition might be particularly difficult to observe behaviourally in patients given a background of general cognitive decline. Such background cognitive 'noise' inevitably increases difficulties with detecting more subtle gene-specific changes in patients, and may explain the apparent difference in effects observed in healthy participants. Importantly, however, our earlier neuropsychological study of ZNF804A suggested, in two large independent samples, that the effects of this genotype differed between healthy participants and controls (a finding which persists in the present slightly enlarged sample).<sup>5</sup> If this is the case, these data highlight the need for caution in extrapolating from findings based solely on healthy participant data to neural mechanisms of illness in patients, at least when considering the effects of ZNF804A.

### Conflict of interest

The authors declare no conflict of interest.

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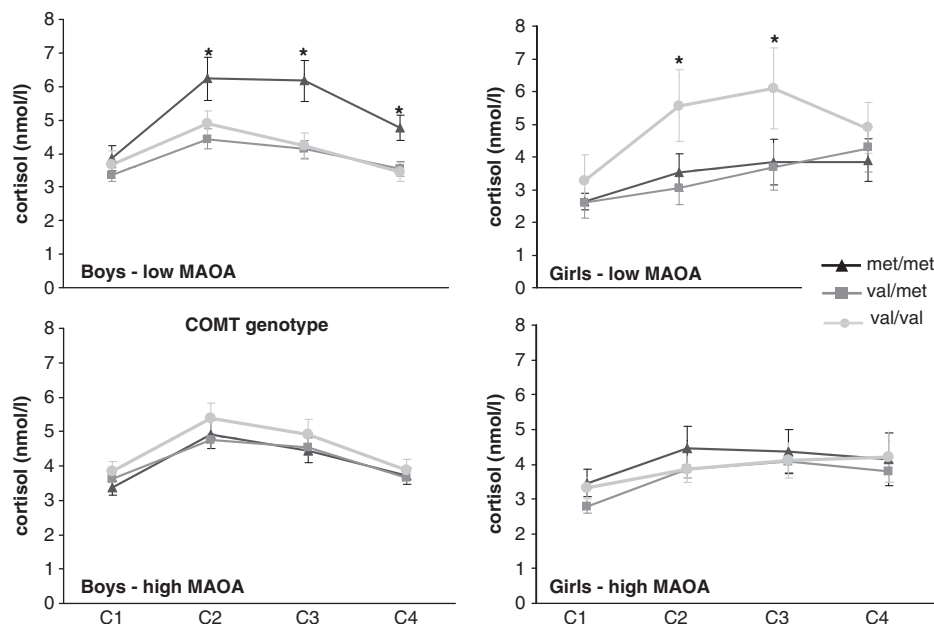
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## Genetically based reduced MAOA and COMT functioning is associated with the cortisol stress response: a replication study

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Variants in the *monoamine oxidase A* (MAOA) and *catechol-O-methyl transferase* (COMT) genes, related to decreased clearance of catecholamines, were associated with an increased hypothalamo–pituitary–adrenal axis response to a social stressor.<sup>1</sup> The aim of the present study was to replicate this finding. Replication of genetic associations is essential before conclusions and causal interpretations can be drawn. The combined effect of the 30-bp length variable number or tandem repeats in the MAOA gene and the COMT *val158met* SNP (rs4680) on cortisol responses to stress was examined in 452 participants of TRAILS (TRacking Adolescents' Individual Lives Survey) (mean age 16.01 years (s.d.=0.94): 38.5% girls, no oral contraceptives users).

Participants performed the Groningen Social Stress Test (GSST, details in ref. 2). Cortisol was assessed from saliva: just before (C1), directly after (C2) and 20 mins (C3) and 40 mins (C4) after the end of the GSST. Depressed mood was assessed just before the GSST with the short Profile of Mood States questionnaire.<sup>3</sup> DNA was extracted from blood samples ( $n=406$ ) or buccal swabs ( $n=46$ ). To avoid elevated cortisol levels, due to venipuncture-related



**Figure 1** Effect of COMT genotype on cortisol level and the cortisol response in boys and girls in the low and high MAOA group. Notes: low = individuals with only 2R, 3R or 5R alleles, high = individuals with at least one 3.5R or 4R allele.<sup>4</sup> Error bars represent standard errors of the mean. The symbol '\*' indicates significant differences between genotype groups. C1 = cortisol level before the stress test, C2 = cortisol level during speech, C3 = cortisol level during arithmetic, C4 = cortisol level 20 min after the stress tests. See Supplementary Table S1 for genotype frequencies.

stress, blood samples were collected during another week as the GSST was assessed. Genotyping call rate was 100% for rs4680 and 98% for the 30-bp variable number or tandem repeats.

MAOA length alleles were divided into 'low' (2R, 3R, 5R) and 'high' (3.5R, 4R), referring to the transcription efficiency of the MAOA gene.<sup>4</sup> Girls were assigned to the 'low' group if they had a 'low' variant at both alleles. Genotype frequencies are given in Supplementary Table S1. In line with Jabbi *et al.*,<sup>1</sup> effects of COMT were tested in low and high MAOA-expressing individuals. Two dummy variables were created, indicating the presence of a *val/met* or *met/met* genotype, respectively, with the *val/val* genotype group, which is assumed to reflect high activity,<sup>5</sup> as the reference group. In case if gender interacted significantly with COMT, *post-hoc* analyses were performed to assess the effect of COMT in boys and girls separately. Repeated-measures General Linear Modeling procedures were performed with the cortisol measures as dependent variables. Cortisol level refers to the mean cortisol concentration across the four samples, and cortisol response to the change in cortisol concentrations during the GSST, as defined by the quadratic within-subject effect. Prestress depressed mood and starting time of the GSST were included as covariates. We corrected for multiple testing using the False Discovery Rate procedure,<sup>6</sup> resulting in an alpha threshold of 0.025.

Associations between the variables are given in Supplementary Table S2. In the low MAOA group, interactions with gender were found for both the

cortisol level and response (Supplementary Table S3a). Gender-stratified analyses (Supplementary Table S3b) indicated that boys with the *met/met* genotype had higher cortisol levels than boys with the *val/val* genotype. Girls with the *val/val* genotype had stronger cortisol responses than the *val/met* girls. In the high MAOA group, COMT genotype did not affect the cortisol measures (Supplementary Table S3c). The effects of COMT and MAOA on the cortisol response are visualized in Figure 1.

Jabbi *et al.*<sup>1</sup> showed that the COMT *met/met* genotype in combination with low MAOA, present in males predominantly, was associated with increased adrenocorticotrophic hormone responses. We replicated this association in adolescent boys with saliva cortisol, a measure physiologically more distant from the central hypothalamo-pituitary-adrenal axis than adrenocorticotrophic hormones, which suggests a causal association. An increased drive on the hypothalamo-pituitary-adrenal axis by higher levels of trans-synaptic catecholamines could be a biological plausible mechanism. The effect of COMT in the low MAOA group differed between boys and girls. The highest cortisol levels and most pronounced responses were observed in *met/met* boys and in *val/val* girls, respectively. This gender difference is in concordance with the hypothesized differential effects of high and low COMT functioning in the development of mental disorders in men and women.<sup>7</sup> Our finding should be interpreted with caution; although our overall sample size was large, the low MAOA genotype group consisted of only 29 girls (relative to

100 boys). Future studies should explore gender-specific effects of functional polymorphic genes involved in the activation of the hypothalamo-pituitary-adrenal axis and the role in stress-related psychopathology.

### Conflict of interest

The authors declare no conflict of interest.

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## Converging evidence for central 5-HT effects in acute tryptophan depletion

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Acute tryptophan depletion (ATD), a dietary technique for manipulating brain serotonin (5-HT) function, has advanced our understanding of 5-HT mechanisms in the etiology and treatment of depression and other affective disorders.<sup>1</sup> A recent review article in *Molecular Psychiatry* questioned the validity of ATD.<sup>2</sup> Although we agree that ATD's effects on 5-HT activity at the molecular level need further clarification, van Donkelaar *et al.*<sup>2</sup> goes too far in challenging whether ATD exerts its effects through serotonergic mechanisms. There is strong evidence that ATD reduces brain 5-HT and disrupts stimulated 5-HT release,<sup>3,4</sup> and converging translational findings support a central role for brain 5-HT in ATD's effects on cognition and behavior.<sup>5–7</sup>

Van Donkelaar *et al.*<sup>2</sup> does not dispute the fact that ATD reduces 5-HT synthesis and brain 5-HT levels.<sup>4</sup> Their arguments converge on two issues. First, they claim that non-serotonergic mechanisms could explain ATD effects, including altered peripheral metabolic processes, cerebrovascular abnormalities and confounding stress effects. Although we welcome additional research to explore these complex alternative pathways, the most parsimonious explanation of ATD's effects on human cognition and behavior is that ATD influences central 5-HT function. ATD has produced results paralleling those following other 5-HT manipulations in humans and animals. For example, ATD has reliable and highly selective effects on emotional processing in humans, inducing a cognitive bias toward negative stimuli and away from positive stimuli.<sup>5</sup> In line with these findings, a recent translational study comparing the effects of citalopram and neurotoxin-induced global 5-HT depletions in rats showed that reducing 5-HT function increased sensitivity to negative stimuli and reduced sensitivity to positive stimuli, whereas enhancing 5-HT function had the opposite effect.<sup>6</sup> Many other equivalent examples abound.<sup>7</sup> These converging findings have been replicated across different laboratories, and support a primary role for brain 5-HT in mediating the effects of ATD.

Moreover, the argument that stress confounds the interpretation of ATD's effects is untenable. ATD studies are placebo-controlled for precisely this reason, so that the unpleasant aspects of the procedure are matched across placebo and depletion conditions. Although we acknowledge it is difficult to examine the effects of ATD (relative to placebo) under